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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/829,968	04/11/2001	Klaus Peter Hirth	038602/1140	1137

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Beth A. Burrous
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, DC 20007-5109

EXAMINER	
HOLLERAN, ANNE L	
ART UNIT	PAPER NUMBER
1642	6

DATE MAILED: 12/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/829,968	HIRTH, KLAUS PETER	
	Examiner	Art Unit	
	Anne Holleran	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed September 20, 2002 is acknowledged. Claims 26 and 27 were added.

Claims 20-27 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

3. The rejection of claims 24 and 25 under 35 U.S.C. 112, first paragraph, for introducing new matter into the specification, is withdrawn in view of the amendment to the claims.

New Grounds of Rejection:

4. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is indefinite because it depends from claim 23, which fails to provide antecedent basis for "the tyrosine kinase receptors".

5. Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation would be required to practice the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

Claims 26 and 27 are drawn to methods for detecting metastasis at a site distal form a primary tumor in a human, where the distal site is a body fluid, comprising administering a labeled ligand that specifically recognizes VEGF, and detecting the labeled ligand in the human, wherein abnormal presence of the labeled ligand indicates overexpression of VEGF in a body fluid and further indicates the presence of metastasis in the human. The body fluid may be blood, serum, urine, lymph or cerebrospinal fluid. Thus, the claims are drawn to methods where the labeled ligand in administered and then its presence detected in a body fluid. The most common route of administration will probably be intravenous. Therefore, the labeled ligand will be present in the blood from the beginning of the operation of the claimed method.

The specification fails to provide working examples of any of the claimed methods of detection, and contemplates detection of metastasis in body fluids that are continuous with the primary tumor. The specification fails to define the scope of abnormal presence of the labeled

ligand for methods where the detection is occurring in a body fluid. Because the claimed methods require administering the labeled ligand to blood, and because most body fluids are in equilibrium with the blood, the ligand would be detectable in most body fluid compartments. Thus, it would require undue experimentation to make a method as claimed because one of skill in the art would first have to determine what levels of ligand constitutes an "abnormal presence" of the ligand in a body fluid compartment.

6. Claims 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boocock (J. Nat. Cancer Inst., 87(7): 506-516, 1995) in view of Ferrara (WO 94/10202; published 11 May 1994).

Claims 20-23 are drawn to methods for detecting metastasis at a site distal from a primary tumor comprising administering to a human a detectably labeled ligand that specifically recognizes VEGF; and detecting the labeled ligand in the human, where abnormal presence of the labeled ligand indicates overexpression of VEGF at a site distal from the primary tumor and further indicates the presence of metastasis in the human. The ligand may be a n anti-VEGF antigody, and VEGF receptor fusion protein or a VEGF receptor conjugated protein. The detection may be by a methods entailing X-ray, CAT-scan or MRI. Claims 24 and 25 are drawn to methods of claim 20 further comprising detecting co-expression of tyrosine kinase receptors involved in angiogenesis, where the receptors may be KDR/flk-1, flt-1 or tek/tie-2.

Boocock teaches that VEGF is detectable immunologically in sites of metastasis, and that VEGF expression is elevated compared to normal tissue (see page 511, 1st col.; and page 507, under Tissue collection and cell culture). Thus, Boocock teaches that VEGF is detectable at a site

that is distal from a primary tumor (a sample of a tissue metastasis is by definition a site that is distal from a primary tumor). Boocock also teaches that flt is immunologically detectable in blood vessels that are adjacent to nests of tumor cells (page513-514, bridging paragraph). Boocock also teaches that cell lines expressing VEGF RNA also express VEGF receptor (flt and KDR) RNA (page 513, 1st col-2nd col., bridging paragraph).

Boocock fails to explicitly teach an in vivo method of detection of VEGF.

Ferrara teaches the use of VEGF antibodies and VEGF receptor proteins in in vivo methods of detection of VEGF and diagnosis (see page 12, lines 26-32; page 11, lines 31 - 37) and teaches that the methods of detection may be nuclear magnetic resonance (MRI is a detection method of nuclear magnetic resonance), or radiology (reads on CAT-scan and X-ray).

Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a method for in vivo detection of VEGF for the detection of metastasis at a site distal from the primary tumor, and also to have made a method that further comprises detection of angiogenic tyrosine kinase receptors, such as flt. One would have been motivated to have made such a method because Ferrara teaches that it is desirable to have a means for assaying for the presence of VEGF in pathological conditions such as cancer, and because Boocock teaches that the VEGF is present in metastatic tumors. One would have had a reasonable expectation of success in making the claimed methods because of the teachings of Boocock that VEGF is present in metastatic tumors, which are by definition a site distal from the primary tumor.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

Anne L. Holleran
Patent Examiner
December 14, 2002

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600